Attorney Docket No. P63187US2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of Philippe Du MESNIL et al.

Serial No.: 10/722,467 Group Art Unit: 1617

Filed: November 28, 2003 Examiner: Yong Soo Chong

For: **PROCESS FOR TREATING LAMENESS BY ADMINISTRATION OF A BISPHOSPHONIC ACID DERIVATIVE**

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Dominique Thibaud, do hereby declare and state that:

1. I am a citizen of France residing in the United States at 14312 Farley Street, Overland Park, Kansas.
2. I am a named inventor of the subject application.
3. I am a Doctor in Veterinary Medicine, currently holding the title and position Director of Development and Pharmaceutical Regulatory Affairs, at Ceva Animal Health, Inc.
4. I am familiar with the rejection—set forth in the final Office Action mailed February 12, 2009—of claims 12-2 1 (Appendix, *infra)* under 35 USC 103(a) for allegedly being obvious over Barbier (US 5,488,041) in view of Huber (US 3,637,641) (hereafter "rejection").
5. With respect to the rejection, I provide—as an expert in the field of the invention—the following analysis and opinion:

   The rejected claims are directed to a treatment for osteoarthrosis-induced lameness in a non-human animal not suffering from fractures. The treatment—as claimed—requires

administering to the non-human animal a compound selected from among multiple, specifically named bisphosphonic acid derivatives and their salts (hereafter, "bisphosphonic acid compound").

According to the statement of rejection, it would have (allegedly) been obvious to the skilled person to use the bisphosphonic acid compound to treat osteoarthrosis-induced lameness as recited in the rejected claims, because (allegedly)

> it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have administered a bisphosphonic acid derivative, for example 4-chlorophenyl thiomethylenebisphosphonic acid, as taught by Barbier et al. to treat lameness in a horse suffering from osteoarthrosis as taught by Huber et al.
>
> A person of ordinary skill in the art would have been motivated to administer a bisphosphonic acid derivative, for example 4-chlorophenyl thiomethylenebisphosphonic acid, as taught by Barbier et al. to treat lameness in a horse suffering from osteoarthrosis as taught by Huber et al. because: (1) Barbier et al. teach broadly that bisphosphonic acid derivatives are useful for treating bone disorders; and (2) Huber at al. teach that bony exostosis, also knows as osteoarthrosis, is a common bone disorder in horses characterized by lameness and difficulty in locomotion or limping. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in treating lameness in horses suffering from osteoarthrosis by administering a bisphosphonic acid derivative, such as 4-chlorophenyl thiomethylenebisphosphonic acid.

(final Office Action, pages 5-6). The statement of rejection is clearly incorrect, for at least the following reasons

In general, one skilled in the art interested in treating lameness caused by osteoarthrosis (OA)—known also as osteoarthritis—simply would not look to a reference such as Barbier, which is directed to the repair of bone fractures, let alone look to Barbier's teachings—directed to treating bone fractures—when seeking to treat an animal "not suffering from bone fractures," as presently claimed. OA is a disease that affects the

joints: it is a degenerative process that not only affects the bone but also the other components of the joint (cartilage and soft tissues). OA progressively alters the normal structure of bone (most often, there is a densification of bone, identified as sclerosis on radiographic images) and of the other joint components. Bone fracture is not a common finding in joints suffering from OA.

Bone repair is a physiological process that occurs after a fracture of the bone. Bone repair is a process that is aimed at producing a new normal bone to fuse together the two fractured pieces of bone. A person skilled in the art would not have expected a useful treatment of the alteration in normal bone structure—induced by OA— would also be useful in promoting the repair of fractured bone (and conversely).

Huber (Abstract) teaches a method of lessening "pain and structural abnormalities associated with post-traumatic arthritis ... by systemic administration of orgotein." Huber (column 2, lines 10-13) teaches "post-traumatic arthritis" in non-human animals is "generally known as bony exostosis." Huber (column 4, lines 1-4) teaches "with continued [orgotein] treatment ... at least some of the structural abnormalities associated with the condition" are lessened.

A bony exostosis (or simply "exostosis") is not also known in the art as "osteoarthrosis," contrary to what is maintained in the statement of rejection. As is well known to the person of ordinary skill in the art, an *exostosis* is "a piece of bone resulting from an excessive bone growth" (*mondofacto dictionary – definition of exostosis*, online at URL: http://www.mondofacto.com/facts/dictionary?query=exostosis, attached hereto). I am aware of no art accepted definition that equates bony exostosis with OA.

Huber (column 2, lines 10-13) does teach with respect to bony exostosis: "In its various clinical manifestations, it is known as [o]steoarthritis of the carpal joints." Huber

specifies the condition *osteoarthritis of the carpal joints*; not "osteoarthrosis," as stated in the rejection.

As mentioned above, OA is not only a bone disease. It is a disease involving all the tissues that compose a joint, i.e., bone, cartilage, synovial fluid, synovium, ligaments, joint capsule, bursa, etc (*mondofacto dictionary – definition of osteoarthritis*, URL: http://www.mondofacto.com/facts/dictionary?query=osteoarthritis, attached hereto). A bony exostosis, however, is exclusively made up of bone (*mondofacto dictionary – definition of exostosis*) and, sometimes, cartilage. Its growth is driven by the bone formation process.

It is true that exostoses can sometimes be observed in an OA afflicted joint. Exostoses can contribute to lameness, in that they can limit the range of movement—about the afflicted joint—due to mechanical discomfort. But, an OA diagnosis is not dependent on the presence of exostoses, nor does the presence of exostoses require an OA diagnosis, i.e., exostoses are by no means found in every OA afflicted joint, and exostoses are found in non-OA afflicted joints.

In both OA and exostosis—both of which are associated with an abnormal, excessive bone formation process—there is often a densification of bone at the joint site. And, Huber teaches that an exostosis is harmful when it occurs in the joint area.

Based on the bone-repair-promoting teachings of Barbier, e.g. (column 3, lines 8-9), "bisphosphonic acid derivatives are useful in bone repair, especially for accelerating it," one skilled in the art would not have expected bisphosphonic acid derivatives to be useful in the treatment of lameness caused by OA. Barbier's teachings imply that there is some unknown, and unexpected, property/activity of the bisphosphonic acid derivatives that is responsible for their ability to promote bone repair. As taught by Barbier (column 1, lines 8-15), bone repair is a process that is characterized by: (1) a first

step of resorption of damaged bone and cartilage, (2) a second step of cartilage formation, (3) a third step of primary bone formation, and (4) a fourth step of lamellar bone formation. The logical interpretation of the bone-repair-promoting effect described by Barbier is that, unexpectedly, bisphosphonic acid derivatives promote bone formation. This is the most rational interpretation of the improvement in the quality of the repair and in the rapidity of the repair that can be attributed to the use of the bisphosphonic acid derivatives.

As explained above, Huber teaches a method of lessening structural abnormalities associated with bony exostosis. Likewise, Huber (column 4, lines 1-4) teaches "with continued [orgotein] treatment ... at least some of the structural abnormalities associated with the condition" are lessened.

So, it would not make sense to a person skilled in the art to combine the teachings of Barbier and Huber as stated in the rejection. That is, contrary to the statement of rejection (as set forth above), it would not make sense to a person skilled in the art "to administer a bisphosphonic acid derivative"—which promotes bone formation—"as taught by Barbier et al. to treat lameness in a horse ... as taught by Huber et al."—which requires lessening bone formation.

Combining the teachings of Barbier and Huber is contraindicated. A person skilled in the art would find use of a bisphosphonic acid derivative (as in Barbier) contraindicated in the Huber method, which achieves lessening of the pathological bone growth associated with bony exostosis. Bisphosphonic acid derivatives, as taught and used by Barbier, promote bone growth; consequently, administering a bisphosphonic acid derivative to a non-human animal suffering from bony exostosis—instead of orgotein—as taught by Huber, would exacerbate the bony-exostosis-induced "lameness," the

"clinical improvement" of which is an objective according to Huber (column 3, lines 63-64).

Huber clearly shows that "orgotein" is useful in treating bony exostosis precisely because it lessens the growth of bone. As exemplified in Huber Examples 1, 2, 4, 7, 8, and 14, X-ray examination post orgotein administration revealed reduced size or shape of bony exostosis. Based on Barbier's teachings, bisphosphonic acid derivatives do exactly the opposite of what Huber obtains—by using orgotein.

Contrary to the rejection's reliance upon Barbier, one skilled in the art who is interested in treating lameness caused by osteoarthrosis would not look to a reference that focuses on the repair of fractures. Moreover, the person skilled in the art would not look to Huber to rectify the rejection's acknowledged deficiencies of Barbier.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth naught.

27 AUG, 2009
Date

Dominique Thibaud

P63187US2 Thibaud Rule 132.wpd

Appendix
Presently Pending Claims

12 Process for treating lameness caused by osteoarthrosis, in a non-human animal suffering from osteoarthrosis and not suffering from fractures, comprising the administration, to the non-human animal, of an effective amount of a bisphosphonic acid derivative selected from the group consisting of:

- 1-hydroxyethylidenebisphosphonic acid and its sodium salts;
- 2-pyrid-2-ylethylidenebisphosphonic acid and its sodium salts;
- phenoxymethylenebisphosphonic acid and its salts;
- thiomorpholinomethylenebisphosphonic acid and its salts;
- 4-chlorophenylthiomethylenebisphosphonic acid and its salts;
- 1-hydroxy-2-(3-pyridyl)ethylidenebisphosphonic acid and its sodium salts;
- 1-hydroxy-2-(2-imidazolyl)ethyl-1,1-bisphosphonic acid and its salts; and
- 2-hydroxyethylidene-2-(3-pyridyl)-1,1-bisphosphonic acid and its sodium salts.

13 Process according to claim 12, for treating an animal belonging to the equidae family.

14 Process according to claim 12, for treating a horse.

15 Process according to claim 12, comprising the administration of 0.001 mg/kg to 100 mg/kg of body weight of the bisphosphonic acid derivative.

16 Process according to claim 12, for treating limps in horses, comprising the intravenous administration of 0.01 mg/kg/week to 1 mg/kg/week of tiludronic acid or one of its pharmaceutically acceptable salts.

17 Process according to claim 12, comprising the oral administration of the bisphosphonic acid derivative.

18 Process according to claim 12, comprising the parenteral administration of the bisphosphonic acid derivative.

19 Process according to claim 12, comprising the administration of the bisphosphonic acid derivative in the form of an implant.

20 Process according to claim 12, in which the bisphosphonic acid derivative is 4-chlorophenylthiomethylenebisphosphonic acid.

21 Process for treating lameness caused by osteoarthrosis, in a horse suffering from osteoarthrosis and not suffering from fractures, comprising the administration, to the horse, of an effective amount of 4-chlorophenylthiomethylene-bisphosphonic acid or its sodium salt.

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exostosis

medical dictionary

A non cancerous growth on the surface of a bone, usually with a cartilage cap, that is due to long-term irritation as a result of osteoarthritis, infections, or trauma.

(09 Oct 1997)

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osteoarthritis — medical dictionary

<pathology> Noninflammatory degenerative joint disease occurring chiefly in older persons, characterised by degeneration of the articular cartilage, hypertrophy of bone at the margins and changes in the synovial membrane. It is accompanied by pain and stiffness, particularly after prolonged activity.

Origin: Gr. Arthron = joint

(11 Mar 2008)

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